Regulation of low-density lipoprotein subfractions by carbohydrates

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Abstract: PURPOSE OF REVIEW: This article aims at reviewing the recent findings that have been made concerning the crosstalk of carbohydrate metabolism with the generation of small, dense low-density lipoprotein (LDL) particles, which are known to be associated with an adverse cardiovascular risk profile. RECENT FINDINGS: Studies conducted during the past few years have quite unanimously shown that the quantity of carbohydrates ingested is associated with a decrease of LDL particle size and an increase in its density. Conversely, diets that aim at a reduction of carbohydrate intake are able to improve LDL quality. Furthermore, a reduction of the glycaemic index without changing the amount of carbohydrates ingested has similar effects. Diseases with altered carbohydrate metabolism, for example, type 2 diabetes, are associated with small, dense LDL particles. Finally, even the kind of monosaccharide the carbohydrate intake consists of is important concerning LDL particle size: fructose has been shown to alter the LDL particle subclass profile more adversely than glucose in many recent studies. SUMMARY: LDL particle quality, rather than its quantity, is affected by carbohydrate metabolism, which is of clinical importance, in particular, in the light of increased carbohydrate consumption in today's world.

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Regulation of low-density lipoprotein subfractions by carbohydrates

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Summary

Purpose of review: This article aims at reviewing the recent findings that have been made concerning the crosstalk of carbohydrate metabolism with the generation of small, dense low-density lipoprotein (sdLDL) particles, which are known to be associated with an adverse cardiovascular risk profile.

Recent findings: Studies conducted during the past few years have quite unanimously shown that the quantity of carbohydrates ingested is associated with a decrease of LDL particle size and an increase in its density. Conversely, diets that aim at a reduction of carbohydrate intake are able to improve LDL quality. Furthermore, a reduction of the glycemic index without changing the amount of carbohydrates ingested has similar effects. Diseases with altered carbohydrate metabolism, e.g. type 2 diabetes, are associated with sdLDL particles. Finally, even the kind of the monosaccharide the carbohydrate intake consists of is important concerning LDL particle size: Fructose has been shown to alter the LDL particle subclass profile more adversely than glucose in many recent studies.

Summary: LDL particle quality, rather than its quantity, is affected by carbohydrate metabolism, which is of clinical importance in particular in the light of increased carbohydrate consumption in today's world.

Keywords

Low-density lipoprotein, Carbohydrates, Fructose, Cardiovascular risk

Introduction

In the past years, a close link of the quality (size and density) rather than the quantity of low-density lipoprotein (LDL) particles with carbohydrate metabolism has been characterized. Due to the changes in dietary habits that took place during the past decades, in particular human carbohydrate metabolism faces numerous challenges in today's world and may, if disturbed, affect cardiovascular health not only directly, but also by altering lipid profiles towards a more atherogenic pattern.

LDL particles are heterogeneous and can be separated based on their size and density in several subclasses using ultracentrifugation, nondenaturing gradient gel electrophoresis (GGE), nuclear resonance spectroscopy (NMR) and ion mobility [1]. Based on the ultracentrifugation pattern of LDL particles, at least four major subspecies can be classified: large (LDL-I), medium (LDL-II), small (LDL-III) and very small (LDL-IV) particles with increasing density along this classification. In addition to the classification of LDL particles into distinct subclasses, measurement of the LDL peak size helps to characterize the atherogenicity of these particles and to assess the individual cardiovascular risk, particularly in patients with disturbed glucose metabolism.

This article aims at throwing a light at the crosstalk between carbohydrate metabolism and the generation of these different subclasses of low-density lipoprotein particles.

The impact of different LDL subclass profiles on cardiovascular health

A phenotype with predominance of small, dense LDL particles is associated with an about 3-fold increased risk of coronary artery disease. This has already early been shown in studies of myocardial infarction as well as coronary disease without infarction in the general population. The aim of more recent studies was to confirm this in specific populations. Patients on hemodialysis form one of these important subpopulations because they are at a

high risk for atherosclerosis. In this group, the link between sdLDL and coronary artery disease [2] and also survival [3] has recently been established.

The importance of LDL subclass distribution compared to total LDL cholesterol levels

One of the most important questions when considering the clinical value of LDL particle size measurements and the assessment of the risk that is associated with a specific LDL lipid profile is whether this adds relevant information to the information that is already provided by traditional lipid profiles. A systematic review published in 2009 concludes that previous studies have not “determined whether any measures of LDL subfractions add incremental benefit to traditional risk factor assessment” [4].

However, more recent studies have added relevant data on the predictive information of LDL particle size that extends its value beyond the information of traditional lipid profiles. Our group has shown that an elevation of small LDL (as assessed by GGE) was associated with a significant increase in the incidence of cardiovascular events during a 2-year follow-up in patients with non-coronary atherosclerosis independently of standard lipid measurements and other risk factors [5]. Another group demonstrated that the amount of small LDL particles in patients with acute ischemic stroke is associated with disease status, as well as total and in-hospital mortality, independently of other lipids and standard risk factors [6]. In addition, common carotid artery intima-media thickness (IMT) as a surrogate endpoint for cerebrovascular disease was shown to be independently associated with small dense LDL [7]. Similarly, another study confirmed small dense lipoprotein particles to be the strongest predictor of carotid atherosclerosis assessed by IMT compared with other lipid parameters [8]. Further, in 172 patients with type 2 diabetes mellitus, low-density lipoprotein particle size was independently associated with carotid IMT regardless of antidiabetic and lipid-lowering medications [9]. Similar findings have been obtained concerning the value of LDL particle size in predicting coronary artery stenosis by coronary CT scanning or coronary angiography [10]. Finally, in patients on hemodialysis, recent data emphasizes the superiority of LDL

particle size compared to traditional lipid profiles when identifying patients at risk for coronary artery disease [11].

Oxidation and glycation of LDL cholesterol particles

Different mechanisms are proposed to contribute to the more atherogenic characteristics of small dense LDL particles. In addition to the higher susceptibility of these particles to oxidative modification [12], there is growing evidence that they are also more prone to glycation [13].

The generation of different LDL subclasses

Different pathways in the processing of particles with higher density (very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL)) are thought to be the mechanism influencing the size- and density-distribution of low-density lipoprotein particles [14]. Triglyceride availability in turn seems to play an important role in the determination of these pathways. In hypertriglyceridemia, the formation of small, dense LDL particles is favoured, while there is an increased exchange of triglycerides from triglyceride-rich lipoproteins to LDL and HDL particles in exchange of cholesteryl esters through the action of cholesteryl ester transfer protein (CETP) [15]. This process results in the generation of very low-density lipoprotein particles enriched in cholesteryl esters and gives rise to smaller, triglyceride-rich low-density lipoprotein particles. In accordance with the assumptions concerning these pathways, many studies have shown a strong correlation of increased plasma triglycerides with a decreased size and increased density of the predominant LDL subspecies.

The role of insulin in VLDL secretion

Concerning carbohydrate metabolism, insulin secretion as well as the tissue response to insulin seems to play a central role in the production of large, triglyceride rich VLDL particles,

and most importantly for the production of small, dense low-density lipoprotein particles. Numerous studies have assessed the question whether hyperinsulinemia or insulin resistance is the essential pathophysiologic condition to induce the hepatic VLDL overproduction [16]. From experiments conducted in cell culture, it is known that acute exposure to insulin suppresses hepatic VLDL production by many mechanisms [17, 18], however, this effect is abolished or even reversed when insulin secretion is prolonged. In contrast, a quite elegant new study that compared the production of VLDL apolipoprotein B in controls and insulin resistant individuals with patients suffering from insulinoma provides evidence that hyperinsulinema alone is not sufficient to induce VLDL apolipoprotein B overproduction [19] *. Thus, it seems that at least some degree of insulin resistance is necessary for VLDL production. In line with these findings, recent data comparing basal and insulin mediated VLDL-triglyceride kinetics in patients with type 2 diabetes with those in healthy men by hyperinsulinemic euglycemic clamp technique found that increased VLDL-triglyceride concentrations in diabetic men were caused by an increase in their secretion, while the ability of hyperinsulinemia to suppress them was still preserved [20] **.

Carbohydrate intake and LDL particle subclasses

Interventional studies comparing the effects of low and high carbohydrate diets on LDL found that high carbohydrate diets effect LDL particle size, generating smaller, potentially more atherogenic LDL particles as compared to low carbohydrate diets.

Short-term interventions

Such results were observed already during a recent short-term study, where isocaloric diets with either high fat / low carbohydrate or low fat / high carbohydrate content were compared (crossover design) in twelve healthy man [21] * during 3 days. After the low fat / high carbohydrate diet, LDL particle size was significantly lower, while particle size distribution

shifted towards smaller particle size. These changes in LDL particle size and density were thought to be the consequence of an observed increase in large triglyceride rich VLDL particles and serum triglycerides, which both are of importance in the generation of small dense LDL as mentioned above. However, changes such as those observed in the above-mentioned study have not been observed in another study after just a single meal with different fat content [22].

Long-term interventions

Recent dietary interventions of longer duration provided similar evidence. One study of 4 weeks duration demonstrated a smaller LDL peak size in individuals after a low-fat / high-carbohydrate diet compared to a high-fat / low-carbohydrate diet [23]. A long-term diet intervention over 9 months has been performed in overweight or obese middle-aged adults. Most importantly LDL size increased in this population during a low-carbohydrate diet, whereas no differences were observed during a low-fat diet. The change in body weight did not differ between these two groups [24]. Therefore, probably when LDL size is already decreased no further decrease can be expected in overweight or obese subjects during a low-fat meal. Further, a Mediterranean-style diet with decreased carbohydrate intake, but also a slight decrease in fat intake (with a shift to the intake of monounsaturated fatty acids) as well as an increase in protein intake has been shown to increase the mean size of LDL particles [25].

Defective carbohydrate metabolism and LDL particle subclasses

Early investigations already reported a more than twofold higher prevalence of the type B lipid profile (which is characterized by the predominance of smaller, denser LDL particles) in patients with type 2 diabetes mellitus (52 % of patients vs. 24 % in the control group).

LDL particles and insulin resistance

The size and density of LDL particles is closely related to insulin resistance. Despite of higher weight being associated with decreased LDL particle size [26], states of insulin resistance, as the polycystic ovary syndrome (PCOS) are associated with a decreased LDL particle size independently of weight [27]. Of interest, a study that investigated the effects of genetic risk loci for type 2 diabetes or hyperglycemia on lipoprotein subclasses in nondiabetic individuals concluded that only a limited number of these risk loci significantly affect lipoprotein metabolism [28]. This supports the hypothesis that an initiation of the cascade ultimately leading to insulin resistance and type 2 diabetes is necessary for significant changes of LDL particle quality.

Different carbohydrates differentially affect LDL quality

Because of the increasing evidence that different carbohydrates differentially affect triglyceride metabolism and insulin resistance [29], differences in their association with LDL particle quality have been tested in recent studies.

Fructose and LDL particle size

Frucose is well known to increase triglyceride levels and to adversely affect insulin sensitivity. Plasma triglycerides are increased by a stimulated hepatic de novo lipogenesis [30] as well as a decreased VLDL-triglyceride clearance [31]. Both these effects are very likely to contribute to an increase in small dense LDL particles as described above. Of interest, it could be shown that such alterations as increased VLDL-triglyceride were more pronounced in healthy subjects with a family history of type 2 diabetes compared with those without such a genetic background when challenged with fructose ingestion [32]. If glucose and fructose consumption were compared directly during a 10 week diet study, indices of postprandial triglycerides (23-hour AUC, triglyceride exposure and postprandial triglyceride

212 peak, but not fasting triglyceride) increased after fructose, but not after glucose consumption.
213 Concomitantly, there was an increase in small dense LDL particles [33]. Of interest, the
214 specific effects of fructose on VLDL-triglyceride can be neutralized by combined ingestion of
215 fat and fructose (with fat alone decreasing VLDL-triglyceride) [34] * and are gender specific
216 with a more pronounced effect in males compared with premenopausal women [35].
217 Today, most fructose is consumed in the form of high fructose corn syrup, which is used as
218 an artificial sweetener in sugar sweetened beverages in many countries. A study assessed
219 whether there are differences in the lipid profile after consumption of high fructose corn syrup
220 compared with the lipid profile after consumption of fructose or glucose alone [36] **.
221 Whereas indices of postprandial triglycerides were only increased after fructose and high
222 fructose corn syrup, small dense lipoprotein particles were increased after all the
223 interventions.
224 When we investigated the association of fructose consumption with LDL quality in overweight
225 schoolchildren, we found that fructose ingestion predicts LDL particle size in this population
226 [37]. Recently we investigated in a randomized intervention study whether the effects of
227 fructose consumption (in the form of sugar sweetened beverages, SSB) during a short period
228 of only three weeks differ significantly from those of other sweeteners (glucose or sucrose).
229 Indeed, LDL particle size was significantly lower after consumption of SSB sweetened with
230 fructose or sucrose compared with those sweetened with glucose [38] **.
231
232 *Glycemic index and LDL particle size*
233 Not only the kind of the monosaccharide, but also the form in which a certain quantity of
234 carbohydrates is provided seems to influence LDL particles. Ingestion of food with a high
235 glycemic index is associated with dyslipidemia. Plasma triglycerides have been shown to be
236 higher in participants of a large observational study who consumed carbohydrates with a
237 higher glycemic index – interestingly, this association was independent of age, BMI, exercise
238 and the intake of other macronutrients [39]. Such observations could be extended to an

association of a high glycemic index with an unfavourable lipoprotein subclass profile in a more recent study [40].

Conclusion

The quantity of low-density lipoprotein particles remains often unchanged when alterations in carbohydrate metabolism occur, but their quality changes. An increase in carbohydrate ingestion as well as an increase in the glycemic index is associated with a smaller LDL particle size. Furthermore, certain forms of carbohydrates also shift LDL particle subclass distribution towards a more unfavourable profile. Fructose, already in moderate amounts, adversely affects LDL size in interventional studies. Diseases with an impaired carbohydrate metabolism, as the metabolic syndrome and diabetes mellitus, have also been demonstrated to be closely associated with an abundance of smaller, denser LDL particles.

LDL size and subclass distribution integrate many aspects of carbohydrate intake and metabolism with an impact on cardiovascular health that are not adequately reflected by the single measurement of its quantity. Qualitative aspects of LDL particles and subclasses will be of increasing clinical importance in the future, in particular in the light of increased energy and carbohydrate consumption and its detrimental effects on human health.

Key points

- There is evidence that small, dense LDL particles are associated with a higher cardiovascular risk independently of the total LDL cholesterol level.
- The amount or type of carbohydrates ingested modulates the quality rather than the quantity of low-density lipoprotein cholesterol.

- Disturbed carbohydrate metabolism, as seen in type 2 diabetes mellitus, is associated with a more unfavourable LDL particle subclass distribution.
- Isocaloric ingestion of different carbohydrates affects LDL particle size differentially, with a particular decrease seen after fructose ingestion.

Acknowledgements / Conflict of interest

The authors have no relevant conflict of interest to declare.

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